Antibody-Drug Conjugates in Colorectal Cancer: A Scoping Review of Current Evidence and Emerging Clinical Insights

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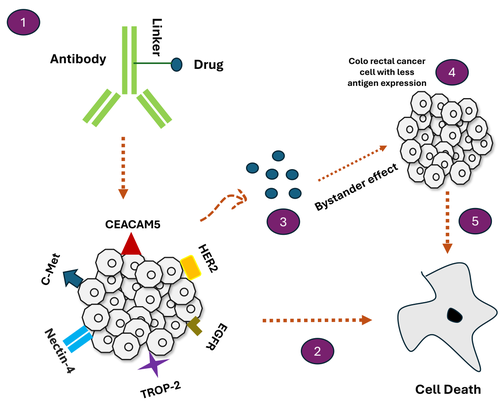
INTRODUCTION

- Colorectal cancer (CRC) is the second leading cause of cancer deaths globally (1).
- Despite advances in treatment, many patients with advanced/metastatic CRC experience poor survival, systemic toxicity, and therapeutic resistance (1).
- Antibody–drug conjugates (ADCs) target tumor antigens (e.g., HER2, TROP2, CEACAM5, C-Met) to deliver cytotoxins selectively, overcoming resistance and reducing off-target effects (2).
- Clinical data on ADCs in CRC remain fragmented, limiting guidance on efficacy, safety, target selection, and resistance mechanisms (2).



1) ADC binds to antigen-expressing CRC cells,
2) Internalized via endocytosis, releasing a cytotoxic payload causing cell death,
3) Bystander effect ,
4) Active drug diffuses into neighboring cells with low antigen expression,
5) Inducing additional tumor cell death.

OBJECTIVES

The objective of this scoping review was to map the current ADC landscape in CRC, summarize clinical trial outcomes and safety profiles, and identify knowledge gaps.

METHODS

Define Scope
- Establish objectives on ADC targets, mechanisms, and outcomes in CRC.

Identify Evidence
- Search databases and registries for relevant preclinical and clinical studies.

Screen & Chart
- Apply selection criteria and capture key ADC attributes and results.

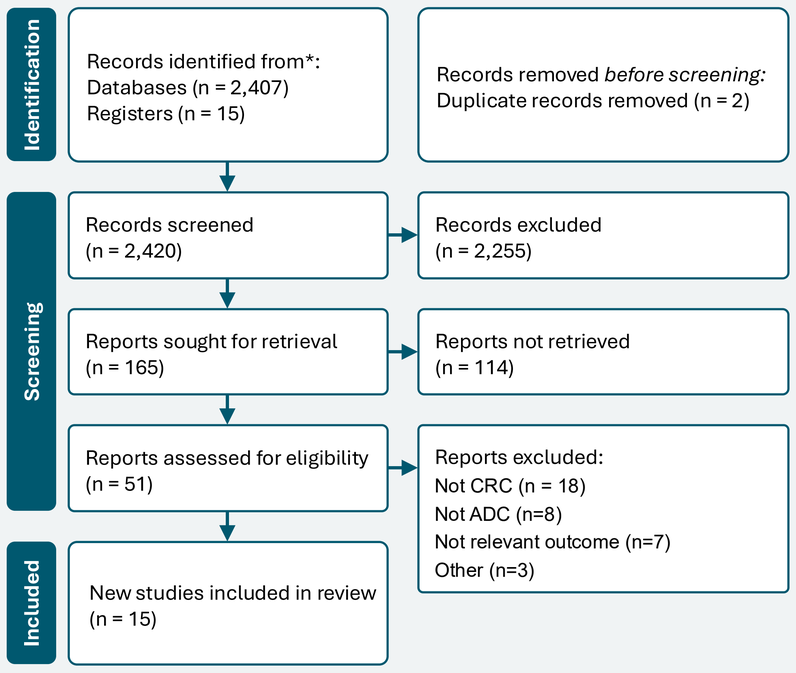
Map Findings
- Categorize by target class, payload, and clinical stage.

Analyze Gaps
- Highlight unmet needs, translational insights, and future research directions.

PCC Element	Inclusion Criteria	Exclusion Criteria
Population	Patients with colorectal cancer (CRC) of any stage (localized, metastatic, or recurrent).	Studies not involving CRC populations.
Concept	Evaluation of **Antibody–Drug Conjugate (ADC)** therapy, including preclinical or clinical investigations demonstrating target engagement, antitumor activity, or safety outcomes.	Studies not involving ADC-based interventions; studies assessing conventional chemotherapy, targeted therapy, or immunotherapy without ADC components.
Context	Peer-reviewed articles, conference abstracts, or registry records (e.g., ClinicalTrials.gov, EU CTR) published between **March 2015 – March 2025**. Both preclinical and clinical (Phase I–III) studies considered.	Publications outside the defined date range; non-peer-reviewed material, editorials, or commentaries without original data.
Outcome Focus	Evidence of **preclinical success** (mechanistic or efficacy data) and/or **clinical findings** on efficacy or safety.	Studies lacking measurable outcomes related to ADC efficacy, safety, or translational success.
Language/ Accessibility	Full-text available in English.	Non-English or inaccessible full-text publications.

Data charting elements: Standardized Excel template including study details, ADC name/target, patient setting, trial phase/status, efficacy (ORR, PFS, OS), safety outcomes, and conclusions.

RESULTS



- 11 ADCs identified targeting HER2, CEACAM5, TROP-2, c-Met, EpCAM, and Globo H.
- HER2-ADCs (e.g., trastuzumab deruxtecan) showed the best activity (ORR ≤45%) with manageable toxicity in biomarker-selected mCRC.
- Others (CEACAM5, TROP-2, c-Met): Modest efficacy (ORR 1–20%, PFS 1.2–6.7 months) due to antigen heterogeneity/suboptimal design.
- Common adverse events including hematologic (neutropenia, anemia), GI events, and occasional ILD, sometimes leading to discontinuation.

Scoping Review Findings – ADC Design Trends in Colorectal Cancer:

Target Expansion
- CEACAM5 and HER2 remain dominant ADC targets, with newer focus on c-Met, ROR1, CDH17, Nectin-4, EpCAM, and TROP-2, signaling diversification in antigen discovery.

Payload Preference
- Topoisomerase I inhibitors lead most constructs, followed by MMAE (microtubule inhibitors) and DNA-crosslinking agents, reflecting ongoing optimization of cytotoxic payload classes.

Clinical Activity
- HER2-directed ADCs (notably trastuzumab deruxtecan) show the highest efficacy (ORR 37–45%, PFS ~7 mo., OS ~15 mo.), while CEACAM5 and TROP-2 agents exhibit modest activity (ORR ≤10%).

Safety Trends
- Common toxicities include hematologic and gastrointestinal AEs, with isolated ILD and infection-related deaths underscoring the need for early safety signal monitoring.

Development Stage
- Most molecules are in Phase I/II stages, focusing on metastatic or advanced CRC, highlighting an exploratory phase for efficacy and target validation.

Emerging Design Shifts
- Innovative ADC architectures (e.g., bispecific constructs, immune-stimulatory linkers) suggest a transition toward next-generation, precision-driven ADCs in colorectal cancer.

Clinical Evidence on ADCs in Colorectal Cancer

ADC Molecule	Target	Sample Size	ORR (%)	PFS / OS (months)	Key Safety Notes
Tusamitamab Ravtansine	CEACAM5	43	Not reported	–	Well tolerated; no deaths
Trastuzumab Deruxtecan	HER2	86	45.3	PFS 6.9 / OS 15.5	GI, hematologic; 3 ILD deaths
Trastuzumab Deruxtecan	HER2	122	37.8	–	Nausea, neutropenia, anemia; 1 ILD death
M9140	CEACAM5	40	10	PFS 6.7	Cytopenias; 1 sepsis death
Sacituzumab Govitecan	TROP-2	31	3.2	PFS 3.9 / OS 14.2	Neutropenia, diarrhea; 1 pneumonia death
Labetuzumab Govitecan	CEACAM5	86	1	PFS 3.6 / OS 6.9	GI AEs, cytopenias; 15% discontinuation
ABBV-400	c-Met	122	15–20	PFS 4–5.3	Cytopenias, fatigue; 9% discontinuation
Anti-EpCAM ADC (MRG003)	EpCAM	61	0	PFS 1.2	Rash, cytopenias; 2 deaths
Trastuzumab Deruxtecan	HER2	20	5	PFS 4 / OS 15.6	Hematologic AEs; 8.5% discontinuation
OBI-999	Globo H	4	–	–	Cytopenias; no deaths

Summary:

- **ADC Molecule:** Ten ADCs identified, mainly CEACAM5- and HER2-directed, with emerging targets (TROP-2, c-Met, EpCAM, Globo H).
- **Target: HER2** and **CEACAM5** dominate; others remain exploratory.
- **Sample Size:** Trials enrolled **4–122 patients**, mostly **early-phase**.
- **ORR (%): HER2 ADCs (37–45%)** show highest efficacy; others range **0–20%**.
- **PFS / OS: PFS 3–7 mo, OS up to ~15 mo**, best with **trastuzumab deruxtecan**.
- **Safety:** Common **hematologic/GI AEs**; few severe cases (ILD, sepsis, pneumonia).

DISCUSSION & CONCLUSION

- HER2-targeted ADCs show the most promise in biomarker-selected metastatic CRC patients.
- ADCs targeting CEACAM5, TROP-2, and c-Met have shown modest efficacy, emphasizing the need for precise patient selection and tumor profiling.
- Safety considerations remain critical: common toxicities include hematologic effects and interstitial lung disease.
- Future strategies: combination therapies, next-generation dual-payload ADCs, and biomarker-guided trials to improve efficacy and tolerability.
- Current evidence is mainly from early-phase trials; this review provides a foundation for clinical decision-making and rational ADC development in CRC.

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